LETTERS AND CORRESPONDENCE

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Retreatment With Low-Dose Cytarabine in Patients With Previous Central Nervous System Toxicity

To the Editor: During the last 10 years, due to high-dose regimens and the treatment of more elderly patients, numerous reports of central nervous system (CNS) toxicity secondary to cytarabine therapy have been published. There is little information about the physiopathology of CNS toxicity, but it seems to be dose-dependent and related to age and previous CNS toxicities [1–5]. With regard to this last feature, there are no reports in the literature that analyze retreatment, with lower doses of cytarabine of patients who have suffered previous CNS toxicity.

A 55-year-old male was diagnosed to have myelodysplastic syndrome 1 year before he transformed to an acute non-lymphoblastic leukemia (AML-M7 of the French-American-British classification). He was treated with a 3 + 7 regimen of cytarabine (200 mg/m^2), continuous infusion daily over 7 days, and daunorubicin (45 mg/m^2) by endovenous bolus on the first 3 days. He developed chemotherapy-induced aplasia over 14 days, and then relapsed with 60% of blasts in bone marrow. He received high-dose cytarabine (2 g/m^2 every 12 hr for 4 days) and mitoxantrone (10 mg/m^2 for 3 days) as an intensification regimen.

Four days after cessation of therapy, he developed progressive cerebellar syndrome characterized by severe ataxia, dysmetria, and dysarthria, with mild obnubilation and disorientation. This clinical picture remained unchanged for 72 hr and then slowly resolved in 1 week. CT scanning and lumbar puncture performed early after onset of the first symptoms were absolutely normal.

By day 31 he had achieved partial remission, with 10% of leukemic blasts on bone-marrow examination along with mild pancytopenia. He was treated with a salvage protocol which included BCNU (200 mg/m^2, day 1), VP-16 (300 mg/m^2, days 2 and 3), amsacrine (100 mg/m^2, days 1–3), and cytarabine (300 mg/m^2, continuous infusion over days 1–4). Tolerance was excellent, and the patient developed no neurologic toxicity. He achieved a complete remission and remains alive and event-free 3 months after cessation of therapy.

Neurotoxicity, resulting from systemic administration of ARA-C, can manifest as encephalopathy, cerebellar dysfunction, and peripheral neuropathy. Cerebellar toxicity is the most frequent manifestation [3]. Cerebellar alterations usually take place between days 3–8, and symptoms include dysarthria, dysdiadochokinesia, dysmetria, and ataxia. Sometimes horizontal nystagmus precedes onset of the syndrome [4]. Although outcome of cerebellar toxicity is variable, the majority of patients recover normal cerebellar function within a few days of withdrawal of treatment.

The CNS toxicity of cytarabine is dose-related: total dose rather than schedule or infusion rate appears to be the main factor in developing CNS toxicity [4]. Some authors have pointed out the importance of the cumulative dose of cytarabine. Age over 50 years, a prior history of CNS disorder, and the presence of meningeal leukaemia have been postulated as risk factors for neurotoxicity.

The incidence of recurrent CNS toxicity appears to be high. Eight out of 13 (57%) patients described in different studies experienced recurrent toxicity [1–3,5]. Some developed CNS toxicity even when low or moderate dose were used [5].

There are no firm guidelines regarding retreatment with cytarabine in patients with previous CNS toxicity. It seems reasonable to make individual approaches and consider the risk/benefit ratio in every clinical situation.

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Rare β-Thalassemia Mutation IVS-II-848 (C-A) First Reported in a Turkish Cypriot Family

To the Editor: Until now about 180 different mutations, affecting many different processes in globin gene expression, have been reported as causes of β-thalassemia [1]. Knowledge of the geographic or ethnic distribution of these mutations facilitates effective prenatal diagnosis programs [2–5].

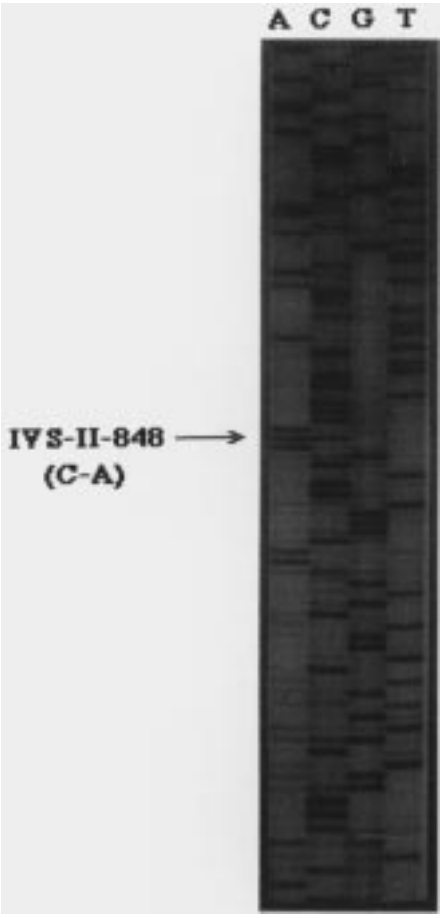

Fig. 1. Genomic sequencing of the heterozygous patient, indicating a C-A substitution at IVS-II-848.

In the Mediterranean region, certain mutations such as IVS-I-110 (G-A) and IVS-I-1 (G-A) predominate in the east, while others such as Cd 39 (C-T) and IVS-I-6 (T-C) predominate in the west. The Turkish Cypriot population has primarily four unique β-thalassemia alleles: IVS-I-110 (G-A), IVS-I-6 (T-C), IVS-I-1 (G-A), and IVS-II-745 (C-G), accounting for 96% of the mutations in this ethnic group. Other alleles are rare, which is indicative of the high degree of genetic homogeneity in this population.

Recently we identified a 25-year-old Turkish Cypriot woman whose hematological analysis revealed mild anemia (HbA, 11.2 g/dl) and hypochromia (MCV, 69 mm; MCH, 21.3 pg). A diagnosis of β-thalassemia carrier status was made, later shown to be inherited from her clinically asymptomatic father. DNA sequencing revealed a C-A substitution at nt 848 of the IVS-2 region (Fig. 1). This was confirmed by allele-specific oligonucleotide hybridization. This mutation was first discovered in an American Black population, but has an estimated frequency of 11% in Egyptians [6]. The mutation abolishes the 3′ consensus sequence and leads to aberrant RNA processing with a resultant β^+ phenotype. The source of mutations in the Turkish Cypriot population is not known, but current haplotype analysis may clarify this.

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